REMARKS

Following entry of this amendment, claims 1-7 and 12-14 will be pending in this application. Claims 1 and 3-7 are currently amended and new claims 12-14 are added. Claims 8-11 are canceled without prejudice. Support for the amendments and new claims can be found throughout the specification and claims as originally filed, e.g., at page 9, lines 10-12 (human); page 11, lines 16-19 (cancer); page 12, line 23, to page 13, line 7 (primed/unprimed); and page 15, lines 16-28 (COX-2 inhibitors).

Applicants request that the Examiner consider and initial the references cited on the Information Disclosure Statement Form PTO-1449 submitted December 21, 2007. The copy of the form returned by the Examiner with the present Office Action was signed at the bottom as considered on January 15, 2009, but the individual references were not initialed, and the form did not include a statement that all the references were considered.

35 U.S.C. § 112, Second Paragraph

Claims 10 and 11 were rejected as allegedly indefinite. Applicants have canceled these claims without prejudice, thus obviating the rejection.

35 U.S.C. § 112, First Paragraph

Claims 1-7 were rejected as allegedly lacking enablement. The Office Action (at page 2) states that the specification "does not reasonably provide enablement for: a method for treating a disease comprising administering dendritic cells and a COX-2 inhibiting compounds." However, the Office Action does acknowledge that the specification is enabling for "a method for treating cancer comprising administering tumor antigen loaded dendritic cells and a COX-2 inhibiting compound."

Applicants do not concede that the claims are not enabled for methods of treating disease conditions other than cancer. However, applicants have amended claim 1 to recite a method for treating cancer, solely to further prosecution, and without prejudice to further applications to pursue claims directed to treating other diseases.

At issue with claim 1 as amended is whether the specification provides enablement for methods of treating cancer with COX-2 inhibitors and dendritic cells that are not tumor antigen loaded, e.g., unprimed dendritic cells. The test for enablement is whether undue experimentation would be required to practice the claimed methods. Factors to determine whether experimentation would be undue include the guidance or direction provided by the application. Here, the application incorporates by reference the published application US 2004/0057935,[1] which demonstrates that unprimed dendritic cells can be utilized for treatment of cancers. See the abstract, paragraphs [0026]-[0027], and Examples 1-9. Essential material may be incorporated by reference to a published patent application for compliance with the requirements of section 112. MPEP § 608.01(p) I.A. The application as filed, therefore, contains sufficient direction or guidance such that one skilled in the art would expect that unprimed dendritic cells could also be used in the claimed methods without undue experimentation.

The Office Action (at page 3) cites Song et al., 2004, Yonsei Med. J., 45:48-52 ("Song") in its discussion of the enablement of the claims. However, it is not apparent to applicants for what purpose Song is cited. Song is not prior art against the instant application, as it was published in 2004, and the instant application claims priority to a provisional application filed October 6, 2003. Applicants request clarification regarding the Office's use of Song.

35 U.S.C. § 103

Claims 1-5, 8, and 9 were rejected as allegedly unpatentable over Zitvogel et al., 1996, J. Exp. Med., 183:87-97 ("Zitvogel") in view of Harizi et al., 2002, J. Immunol., 168:2255-64 ("Harizi") and Rioux et al., 1998, Cancer Res., 58:5354-60 ("Rioux"). Claims 8 and 9 are canceled herein, mooting the rejection with regard to those claims. Applicants respectfully traverse the rejection of the remaining claims.

[1] The application was originally incorporated by reference as U.S. patent application Ser. No. 10/251,148, filed Sep. 20, 2002. Applicants have amended the specification herein to indicate that the application was published as US 2004/0057935.

At pages 5-6, the Office Action states:

> [I]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer a COX-2 inhibitor such as NS-398, as taught by Rioux et al., in the method of treating cancer by tumor antigen pulsed dendritic cell vaccination of Zitvogel. The ordinary artisan would have been motivated to do so and have a reasonable expectation of success, since Rioux et al. teach that COX-2 inhibitors reduce tumor volume and inhibit tumorigenesis. Additionally, the ordinary artisan would have been further motivated to administer the COX-2 inhibitor along with a dendritic cell vaccine, since Harizi et al. teach that inhibition of COX-2 increases IL-12 production and stimulatory capacity of dendritic cells, and Zitvogel et al. teach that IL-12 production by dendritic cells is crucial to the induction of a tumor protective Th1 immune response.

The Office has cited Zitvogel as disclosing "that tumor peptide pulsed dendritic cells can be administered as a vaccine to induce tumor specific T cells for treating cancer" (page 5). At the same page, the Office Action admits that Zitvogel does not "teach administering a COX-2 inhibitor."

To fill this clear gap in Zitvogel, the Office Action alleges that Rioux describes the administration of COX-2 inhibitors for cancer treatment. However, Rioux does not teach treatment of cancer using COX-2 inhibitors, but rather discloses the prevention of tumorigenesis by the tobacco carcinogen NNK. Rioux reports experiments in which NS-398 reduced tumorigenesis due to NNK by 34% (see Table 1; p. 5359, left column). This reduction in tumorigenesis was attributed primarily to inhibition of COX-2's bioactivation of NNK, which is required for its carcinogenic activity (p. 5359, right column; p. 5354, right column). Some effect of NS-398 on cell proliferation was observed on cell lines in vitro, but this effect was observed at concentrations (115-140 μM) that were higher than those achievable by nontoxic doses in mice (p. 5358, left column; p. 5359, left column). Additionally, those doses at which a cell proliferation effect were observed are significantly higher than the 3.8 μM IC_{50} of NS-398 for COX-2 (see Exhibit A). At a concentration of 25 μM of NS-398, closer to the IC_{50} for COX-2, the authors of Rioux observed less than 5% growth inhibition for either cell line (p. 5358, left column). The implication of these findings to one of skill in the relevant art is that the growth inhibitory effect observed in Rioux is not linked to inhibition of COX-2. By contrast, the present

inventors observed activity of NS-398 in human cells at a concentration of 10 μM, consistent with an effect of COX-2 inhibition (see Examples 1, 13, and 14).

Applicants submit that Rioux is silent with regard to the treatment of cancer using COX-2 inhibitors and relates only to the prevention of chemically induced tumorigenesis. Because Rioux relates only to prevention of tumorigenesis and NS-398 was not shown to inhibit cellular proliferation at concentrations at which it inhibits COX-2, one of ordinary skill would not have been motivated by Rioux to even attempt to treat human cancers with COX-2 inhibitors.

Harizi, too, is silent regarding cancer treatment using COX-2 inhibitors. Harizi investigates the effect of exogenous lipopolysaccharide or prostaglandin E_2 on maturation of mouse dendritic cells *in vitro*. The authors of Harizi found that COX-2 inhibitors could suppress the effects of lipopolysaccharide, prostaglandin E_2, or IL-10 on dendritic cell function. However, COX-2 inhibitors were not administered to dendritic cells without these other molecules. Lipopolysaccharides are bacterial endotoxins that can elicit immune responses in mammals, and are not relevant to treatment of cancer. The Office Action has alleged no link between cancer and prostaglandin E_2 or IL-10. The only mention of prostaglandin E_2 in the Action is in reference to Rioux, which relates only to tumorigenesis, and not to the treatment of a diagnosed cancer.

Further, Harizi is ambiguous with regard to the use of COX-2 inhibitors for treating humans. Harizi describes experiments with cultures of mouse dendritic cells in which a COX-2 inhibitor was shown to inhibit upregulation of specific subtypes of PGE_2 receptors by lipopolysaccharide (see p. 758, Figs. 1-2). Harizi also indicates that PGE_2 (a product of the COX-2 enzyme) has a "complex biology in the immune response" and can have either stimulatory or inhibitory effects on activation of dendritic cells depending on the context (p. 760, right column). Harizi further states that "[o]ur finding is not in agreement with studies using human macrophages or DC; when considering the effects of IL-10 on DC phenotype and function, one should keep in mind that mouse and human DC populations are obviously not the same" (p. 2662, left column). Based on the disclosure of Harizi, which relates to mouse cells, it would have been very difficult for one of ordinary skill to predict the effect of the combination

of a vaccination of dendritic cells for the treatment of cancer and administration of a COX-2 inhibitor in a human patient.

Applicants submit that a *prima facie* case of obviousness has not been made. None of the cited references teaches or suggests treatment of cancers with COX-2 inhibitors. Further, Harizi suggests that its findings may not be applicable to humans, such that there would not have been a reasonable expectation of success in combining the references.

Additionally, none of the references teaches or suggests the use of unprimed dendritic cells, as recited in new claim 13, or the COX-2 inhibitors celecoxib, rofecoxib, valdecoxib, and meloxicam, as recited in new claim 14. Because the cited references do not teach or suggest all the claim limitations and there does not appear to have been a reasonable expectation of success in combining the references, applicants submit that the claims would not have been obvious over the combination of Zitvogel, Harizi, and Rioux.

Claims 6, 7, 10, and 11 were rejected as allegedly obvious over Zitvogel, Harizi, and Rioux, and further in view of Yu et al., 2001, Cancer Res. 61:842-847 ("Yu"). As described above, Zitvogel, Harizi, and Rioux fail to teach or suggest the treatment of cancers with COX-2 inhibitors. Yu is silent regarding COX-2 inhibitors and therefore does not remedy the deficiency. Therefore, no *prima facie* case of obviousness has been made regarding claims 6, 7, 10, and 11, and applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants submit that the claims are in condition for allowance and such action is requested. This response is being submitted with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 22862-0003US1.

Respectfully submitted,

Date: July 27, 2009

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EXHIBIT A

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Product Information

NS 398 | **Cat. No: 0942** | **Batch No: 2**

***N*-[2-Cyclohexyloxy-4-nitrophenyl]methanesulfonamide**

Description: Selective cyclooxygenase-2 inhibitor (IC_{50} values are 3.8 and > 100 µM for COX-2 and COX-1 respectively). Induces apoptosis in colorectal tumor cells and elevates COX-2 protein expression *in vitro*. Orally active and non-ulcerogenic analgesic and anti-inflammatory *in vivo*.

Physical and Chemical Properties:

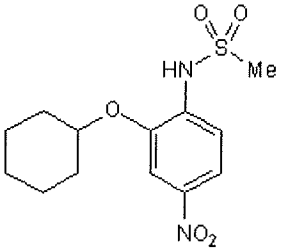
Batch Molecular Formula: $C_{13}H_{18}N_2O_5S$

Batch Molecular Weight: 314.36

CAS Number: [123653-11-2]

Physical Appearance:

Batch Molecular Structure:



Storage: Store at RT

Solubility & Useage Info:
DMSO to 100 mM

Stability and Solubility Advice:
Some solutions can be difficult to obtain and can be encouraged by rapid stirring, sonication or gentle warming (in a 45-60°C water bath).

Information concerning product stability, particularly in solution, has rarely been reported and in most cases we can only offer a general guide. Our standard recommendations are:

SOLIDS: Provided storage is as stated on the product label and the vial is kept tightly sealed, the product can be stored for up to 6 months from date of receipt.

SOLUTIONS: We recommend that stock solutions, once prepared, are stored aliquoted in tightly sealed vials at -20° C or below and used within 1 month. Wherever possible solutions should be made up and used on the same day.

Other Information:

Not for sale in the USA.

Batch 2 is the re-QC of batch 1 (was previously patent restricted and had to be withdrawn from sale)

References:

Futaki *et al* (1993) NS-398, a novel non-steroidal anti-inflammatory drug with potent analgesic and antipyretic effects, which causes minimal stomach lesions. Gen.Pharmacol. ***24*** 105. **Futaki** *et al* (1994) NS-398, a new anti-inflammatory agent, selectively inhibits prostaglandin G/H synthase/cyclooxygenase (COX-2) activity *in vitro*. Prostaglandins ***47*** 55. **Elder** *et al* (2002) The MEK/ERK pathway mediates COX-2-selective NSAID-induced apoptosis and induced COX-2 protein expression in colorectal carcinoma cells. Int.J.Cancer ***99*** 323.